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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/783,931	02/15/2001	David Ish-Horowicz	7326-122	8177
20583	7590	03/09/2004	EXAMINER	
JONES DAY 222 EAST 41ST STREET NEW YORK, NY 10017			KAUFMAN, CLAIRE M	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/783,931	<b>Applicant(s)</b> ISH-HOROWICZ ET AL.	
	<b>Examiner</b> Claire M. Kaufman	<b>Art Unit</b> 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 25 September 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 29-32, 60, 61, 99-136 and 138-145 is/are pending in the application.
- 4a) Of the above claim(s) 106, 111, 112, 115, 119, 120, 127, 137, 140 and 141 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 29-32, 60, 62, 99-105, 107-110, 113, 114, 116-118, 121-126, 128-136, 138, 139 and 142-145 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 29-32, 60, 61, 99-136 and 138-145 are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 July 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>9/25/03</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election with traverse of Group I, species SEQ ID NO:65, in the paper filed on 9/23/03, is acknowledged. The traversal is on the ground(s) that there are generic claims (29-32, 60, 61, 100-104, 107-109, 113, 114, 116-118, 121-125, 129-138 and 142-145), contrary to the Examiner's statement that no claims are generic. This is not found persuasive because it is maintained that there are no generic claims and claims such as 29 are improper Markush groups with species having no requirement for conserved structure or function. Because the specification says the nucleic acids listed may be read in any one of the three open reading frames (see, for example, the Brief Description of Figure 11), this necessarily carries over to hybridizing nucleic acids if no particular reading frame is specified. Therefore, while claimed antibodies might cross-react with more than one species in a claim, they are distinct.

The requirement is still deemed proper and is therefore made FINAL.

Claims 115, 119, 120 and those portions of the remaining claims of Group I for which the Delta protein is not or does not comprise SEQ ID NO:65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. It does not appear that neither SEQ ID NO:23 (a human fragment) nor SEQ ID NO:12 (mouse) comprises SEQ ID NO:65. As a result, claims 106, 111, 112, 127, 140 and 141 are also drawn exclusively to non-elected species and are withdrawn from further consideration. Claim 137 drawn to Group II is also withdrawn.

In response to Applicants' query about the assignment of claim 138 to only Group II, the original restriction lists claim 138 in both Groups I and II.

### ***Specification***

The disclosure is objected to because of the following informalities: there are numerous errors in sequence identifiers cited throughout that specification. For example, on page 87, line 8, it is stated that Figure 12B shows the nucleotide sequence of SEQ ID NO:33. This is not correct since SEQ ID NO:33 is a 40 amino acid long sequence. in lines 11-13, reference to SEQ

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ID NOS:34-36 appears to be incorrect since these sequences are much too short to be full reading frames. Also, on the same page in line 21-22, Figure 14 is said to comprise, respectively, SEQ ID NOS:39-65. Again, this is incorrect because elsewhere in the specification (*e.g.*, Brief Description of Figures 14A-B) and in the claims SEQ ID NOS: 65-80 are stated as being shown in Figure 14. The entire specification should be reviewed for similar errors.

Appropriate correction is required.

### ***Claim Objections***

Claims 114 and 129 are objected to because of the following informalities: in line 6, “is comprises” is incorrect.

Appropriate correction is required.

Claims 29-32, 60, 61, 99-136 and 138-145 are objected to as being drawn to or included non-elected species.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 60, 61, 104 and dependent claims 99, 100, and 102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 61 is indefinite because the metes and bounds cannot be determined because of the use of the term antibody “derivative”. While the specification provides a non-limiting example as a fragment (p. 29, line 13), no definition of the term is provided and recites “a fragment or derivative”, which brings added confusion when the claim is read in light of the specification.

Claims 32 and 104 are indefinite because it is not clear what a “molecule” (line 1) comprising an antibody is. This is not a common phrase in the art and no clarification could be found in the specification.

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Claims 60 and 61 are indefinite because they recite in line 1, "an amount" of an antibody or fragment. It is not clear what the amount is or what you need an amount for.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 109-110, 113, 114, 116-118, 121-126, 128-136, 138, 139 and 142-145 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindsell et al. (cited by Applicants, #C58) or Henrique et al. (cited by Applicants, #C55) in view of US Patent 5,648,464 (cited by Applicants, #A07).

Lindsell et al. teach the rat Jagged protein and show data to support its role in Notch activation and development. First, sequence analysis reveals substantial homology between Jagged and invertebrate ligands for the LIN-12/Notch proteins (*e.g.*, Fig. 1). Second, in situ hybridization of rat embryos identifies both distinct and overlapping patterns of gene expression for Jagged with those for Notch1, Notch2, and Notch3 (*e.g.*, Fig. 3). Finally, the biological activity of Jagged was tested using a cell culture assay in which Jagged activates rat Notch1 expressed in myoblasts and prevents muscle cell differentiation (*e.g.*, Figs. 5 and 6). Our data support the hypothesis that Notch-ligand interactions function in maintaining mammalian cells in an undifferentiated state. Lindsell et al. do not teach an antibody to rat Jagged.

Henrique et al. teach chicken Delta (C-Delta-1, Fig. 1). It was shown that Delta acts as a ligand for Notch, acting as receptor, both or which are likely to play a key role in vertebrate neurogenesis as they do in *Drosophila* (*e.g.* p. 790, col. 2, second full paragraph). Also, *C-Delta*-

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*I* gene expression is reported to be the earliest marker for prospective neurons (p. 790, col. 2, end of first full paragraph). Henrique et al. do not teach an antibody to chicken delta.

US Patent 5,648,464 teaches "toporythmic protein" Notch, Delta and Serrate, which are developmental proteins that interact with (*e.g.*, col. 10, lines 24-41, col. 3, lines 54-67). Also taught are methods of making antibodies to such proteins. It is stated (col. 19, lines 17-44):

For preparation of monoclonal antibodies directed toward a toporythmic protein sequence, any technique which provides for the production of antibody molecules by continuous cell lines in culture may be used. For example, the hybridoma technique originally developed by Kohler and Milstein (1975, *Nature* 256, 495-497), as well as the trioma technique, the human B-cell hybridoma technique (Kozbor et al., 1983, *Immunology Today* 4, 72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., 1985, in *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96)....

In the production of antibodies, screening form the desired antibody can be accomplished by techniques known in the art, *e.g.*, ELISA (enzyme-linked immunosorbent assay). For example, to select antibodies which recognize the adhesive domaone of a toporythmic protein, one may assay generated hybridomas for a product which binds to a protien fragment containing such domain....

Details of antibody hybridoma preparation involving immunization of a mouse with a fusion protein (*e.g.*, col. 21, lines 29-43). Uses of antibodies produced by the above methods are also discussed (col. 19, 47-58). Such techniques were used to show that Notch coimmunoprecipitated with Delta (Figure 5, lane 4). The monoclonal antibodies are taught in supernatant (col. 22, line 45), and polyclonal sera is taught resusupended in PBS (col. 21, lines 25-28).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods of US Patent 5,648,464 to make antibodies, including purified antibodies for use in assays, to the Jagged ligand taught by Lindsell et al. One would have been motivated to do so in order to conclusively show physical interaction of Jagged with Notch as hypothesized by Lindsell et al. by, for example, immunoprecipitation. Immunoprecipitation, a method old and well known in the art, was shown to have successfully identify a Notch interacting protein in US Patent 5,648,464. It would have been obvious to use any of the methods referenced in US Patent 5,648,464 to make antibodies useful in the elucidation of Jagged function. Rat Jagged of Lindsell et al. shares regions of identity (up to 7 amino acids long) and larger regions of similarity (up to 9 amino acids long) with SEQ ID NO:65 of the instant application. Chicken Delta of Henrique et al. is 98% identical to SEQ ID NO:65. (See attached Sequence Comparision for each.) Because of the shared sequence with SEQ ID NO:65

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of the instant application, one of ordinary skill in the art would reasonably expect one of the numerous antibodies produced by the above methods would bind SEQ ID NO:65. However, for claims with hybridizing language that do not require complete identity to SEQ ID NO:65, the chicken and rat sequences readily meet the structural requirements. Further, because of the low identity of *Drosophila* Delta in comparison with C-Delta-1 of Henrique and SEQ ID NO:65, one would reasonably expect that some, if not a majority of antibodies, that bind C-Delta-1 would not bind *Drosophila* Delta, absent evidence to the contrary.

Claims 29-32, 60, 61, 99-105, 107 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henrique et al. (cited by Applicants, #C55) in view of WO 92/19734 (cited by Applicants, #B12).

Henrique et al. teach chicken Delta (C-Delta-1, Fig. 1). It was shown that Delta acts as a ligand for Notch, acting as receptor, both of which are likely to play a key role in vertebrate neurogenesis as they do in *Drosophila* (e.g. p. 790, col. 2, second full paragraph). Also, *C-Delta-1* gene expression is reported to be the earliest marker for prospective neurons (p. 790, col. 2, end of first full paragraph). Henrique et al. do not teach an antibody to chicken delta.

WO 92/19734 teaches delta and notch proteins as well as antibodies to both (p. 38, line 31, through p. 46, line 20). Purified monoclonal antibody to delta are described (paragraph beginning on p. 45, line 27). It was shown with anti-Notch monoclonal antibodies and anti-Delta polyclonal sera in an aggregation assay that Notch and Delta proteins (p. 73, line 26, through p. 80). Well known methods of making antibodies, screening and purifying are disclosed (first paragraph of p. 40) as well as antibody fragments (second paragraph of p. 40). Also taught are methods of selecting anti-Notch antibodies that do not bind *Drosophila* Notch (p. 40, lines 26-30). The monoclonal antibodies are taught in supernatant (p. 48, line 16, and polyclonal sera is taught resuspended in PBS (p. 45, lines 23-26)

It would have been obvious at the time the invention was made to have an antibody, including an antibody fragment, to C-Delta-1 of Henrique et al. because they showed Delta was both an important vertebrate neuronal marker as well as a key player in the Notch pathway. Also, WO 92/19734 showed that interaction between Notch and Delta could be detected by using

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antibodies thereto. Therefore, the skilled artisan would have desired such antibodies and had well known techniques by which to obtain antibodies to C-Delta 1. Further, because of the low identity of Drosophila Delta in comparison with C-Delta-1 of Henrique (see Figs. 3A-3B of Applicant's instant application for comparison) and SEQ ID NO:65 (see attached sequence comparison), one would have reasonably expected that some, if not a majority of antibodies, that bind C-Delta-1 would not bind Drosophila Delta, absent evidence to the contrary. It would, however, reasonably have been expected to bind SEQ ID NO:65 because of the 98% sequence identity (see attached comparison).

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571)272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571)272-0871.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

March 8, 2004

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COMPARISON OF SEQ ID NO:65 TO Rat Jagged

A56136  
 jagged protein precursor - rat  
 C;Species: Rattus norvegicus (Norway rat)  
 C;Date: 28-Apr-1995 #sequence\_revision 28-Apr-1995 #text\_change 11-Jan-2000  
 C;Accession: A56136  
 R;Lindsell, C.E.; Shawber, C.J.; Boulter, J.; Weinmaster, G.  
 Cell 80, 909-917, 1995  
 A;Title: Jagged: a mammalian ligand that activates Notch1.  
 A;Reference number: A56136; MUID:95211842; PMID:7697721  
 A;Accession: A56136  
 A;Status: preliminary  
 A;Molecule type: mRNA  
 A;Residues: 1-1220 <LIN>  
 A;Cross-references: GB:L38483  
 C;Superfamily: unassigned EGF-related proteins; EGF homology  
 F;379-410/Domain: EGF homology <EGF1>  
 F;492-523/Domain: EGF homology <EGF>  
 F;634-665/Domain: EGF homology <EGF2>

Query Match 50.6%; Score 587; DB 2; Length 1220;  
 Best Local Similarity 47.1%; Pred. No. 3.8e-37;  
 Matches 90; Conservative 32; Mismatches 65; Indels 4; Gaps 2;

Qy	2	FTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVGEEWSQDLHSSGRDLDKY	61
		: : :   :     : :   : : :   : :   :	
Db	127	FAWPRSYTLLVEA--WDSSND--TIQPDSIIEKASHSGMINPSRQWQTLKQNTGIAHFEY	182
Qy	62	SYRFVCDEHYEGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTEPICLPGCDEQ	121
		:           :             :   :         :	
Db	183	QIRVTCDDHYEGFGCNKFCRPRDDFFGHYACDQNGNKTCEMGWGMPECNKAICRQGCSPK	242
Qy	122	HGFCDKPGECKCRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCT	181
		: : :   :       :   :   :   :   :   :   :	
Db	243	HGSCKLPGDCRCQYGWQGLYCDKCIPHPGCVHGTCNEPWQCLCETNWGGQLCDKDLNYCG	302
Qy	182	HHKPCKNGATC	192
		:	
Db	303	THQPCLNRGTC	313